

Enantiospecific Synthesis and Pharmacological Evaluation of a Series of Super-Potent, Conformationally Restricted 5-HT_{2A/2C} Receptor Agonists

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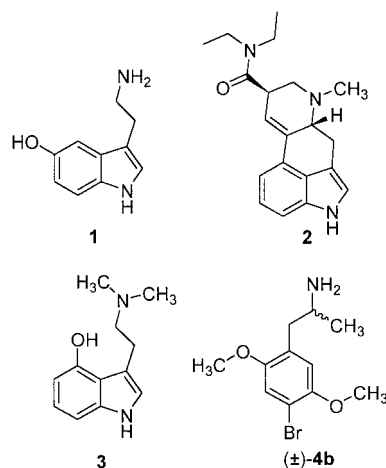
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The affinity of ligands for either the 5-HT_{2A} or 5-HT_{2C} agonist binding site was enhanced by modification of the 2,5-oxygen substituents that are found in typical hallucinogenic amphetamines such as **4b** (DOB). Restriction of the conformationally flexible 2,5-dimethoxy substituents into fused dihydrofuran rings generally resulted in increased potency relative to the parent 2,5-dimethoxy compounds. The pure enantiomers of these arylalkylamines were obtained by enantiospecific synthesis that involved acylation of the heterocyclic nucleus **7** with *N*-trifluoroacetyl-protected D- or L-alanyl chloride, followed by ketone reduction and *N*-deprotection. The enantiomers demonstrated modest stereoselectivity at the two receptors. Several general trends within these classes of new compounds were observed during their pharmacological investigation. For most pairs of optical isomers tested, the *R*-enantiomers of the compounds containing heterocycle **7** bound with only slightly higher affinity than their *S*-antipodes at the 5-HT_{2A} and 5-HT_{2C} receptors. Likewise, functional studies indicated that the *R*-enantiomers generally displayed increased potency compared to the *S*-enantiomers. Aromatization of the dihydrofuran rings of these arylalkylamines further increased affinity and potency. Only a few compounds were full agonists with most of them possessing intrinsic activities in the range of 60–80%. These compounds with a fully aromatic linear tricyclic nucleus are some of the highest-affinity ligands for the 5-HT_{2A} receptor reported to date.

Introduction

Over the past four decades, a vast base of information has been gathered about the physiological role of the neurotransmitter serotonin (5-HT, 5-hydroxytryptamine, **1**). Serotonin is known to be important in physiological systems ranging from hemodynamics and intestinal motility to normal cognition and perceptual processes. Receptors for this endogenous compound have been shown to exist almost ubiquitously throughout the body and especially in the gut and both central and peripheral nervous systems. Molecular biology techniques have led to the discovery of numerous different receptor subtypes for 5-HT, with the possibility of a different physiological role for each.¹ The 5-HT receptor subtype of most interest to our laboratory is the 5-HT_{2A} isoform. Agonist activation of this receptor is believed to be responsible for induction of the unique alterations in consciousness produced by substances such as LSD (*d*-lysergic acid *N,N*-diethylamide, **2**) and psilocin (4-hydroxy-*N,N*-dimethyltryptamine, **3**).²

The molecular determinants for agonist binding to the 5-HT_{2A} receptor have been of great interest to our laboratory in order that we might gain a better understanding of the physiological role of serotonin at this site. One of the factors complicating this research is that structurally diverse classes of compounds retain the ability to bind to and activate this receptor. Chemical classes such as the ergolines (LSD, **2**), tryptamines (psilocin, **3**), and amphetamines (DOB, 4-bromo-2,5-



dimethoxyamphetamine, **4b**) represent a cross-section of compounds that cause hallucinogenesis in humans by putative activation of this receptor. The chemical diversity of these compounds, coupled with the difficulty of melding them into a common pharmacophore, has led to much speculation about the functional topography of the 5-HT_{2A} receptor.

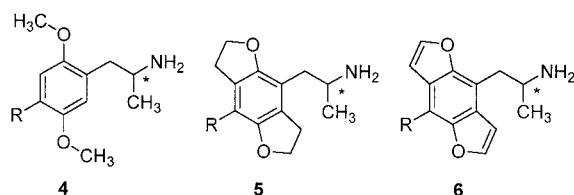
Although it is reasonably well-established that activation of the 5-HT_{2A} receptor by an exogenous ligand leads to hallucinogenesis, agonists that exhibit high affinity for this receptor invariably also bind to the 5-HT_{2C} receptor.¹ This finding has raised questions regarding the involvement of the 5-HT_{2C} receptor in hallucinogenesis.³ The 5-HT_{2A} and 5-HT_{2C} receptors share a relatively high overall sequence homology and, more importantly, are 80% homologous within the transmembrane regions in which the agonist binding

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site is thought to reside.⁴ Thus, it is believed that these two receptors must also share structural features within the agonist binding site. A truly selective agonist would be an invaluable tool for investigating the differences in neuropharmacology between these chemically quite similar receptors.

Recent findings suggest that enough structural variance may exist between the agonist binding sites of the 5-HT_{2A} and 5-HT_{2C} receptors to confer moderate chemical selectivity. Additionally, animal behavioral models of hallucinogenic activity have supported in vitro data showing differential activity for the enantiomers of both amphetamine and LSD analogues.^{5,6} We chose to explore further the importance of stereochemical selectivity in this receptor family through the synthesis and pharmacological evaluation of enantiomerically pure novel arylalkylamines.

We have recently reported the synthesis and preliminary pharmacological analysis of several semirigid analogues of DOB (\pm -**4b**) and related amphetamines.⁷⁻⁹ As a continuation of our studies of these extremely potent 5-HT_{2A/2C} receptor agonists, we present here the enantiospecific synthesis and pharmacological evaluation of a series of semirigid compounds. These compounds incorporate either a tetrahydrobenzo[1,2-*b*:4,5-*b'*]difuran heterocycle in place of the phenyl ring of amphetamines, as in the **5** series, or the fully aromatic benzo[1,2-*b*:4,5-*b'*]difuran counterpart, as in the **6** series. Specifically, the tricyclic nucleus was substituted at the 4- and 8-positions to generate arylalkylamine analogues of 2,5-dimethoxyamphetamine (2,5-DMA, **4a**), DOB (**4b**), and 2,5-dimethoxy-4-trifluoromethylamphetamine (DOTFM, **4c**). The chiral side chain was derived from the enantiomers of alanine. Both the *R*- and *S*-enantiomers of the six arylalkylamine structures were synthesized and evaluated pharmacologically.

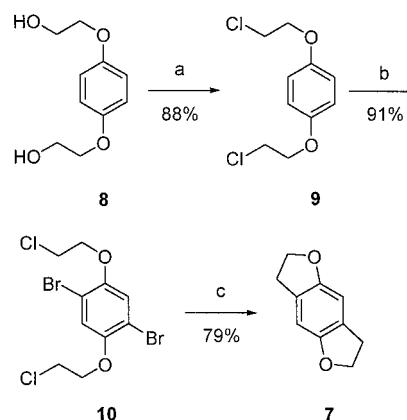


Chemistry

An important intermediate in the synthetic scheme employed to produce these compounds is the heterocyclic nucleus tetrahydrobenzo[1,2-*b*:4,5-*b'*]difuran (**7**).¹⁰ Although our previously reported synthesis of this compound required only three steps and gave a useful yield,¹¹ the straightforward improvements reported here (Scheme 1) provided **7** in 63% overall yield beginning with commercially available 1,4-bis(2-hydroxyethoxy)-benzene (**8**).

To effect the Friedel–Crafts acylation of **7**, our synthetic pathway (Scheme 2) required the acid chloride of optically pure D- or L-alanine (**11**). (Only the *R*-enantiomers are shown in the scheme.) Protection of the amino group of (*R* or *S*)-**11** to afford trifluoroacetamide (*R* or *S*)-**12** was accomplished following a previously reported procedure.¹² This very hygroscopic solid was then converted to the acid chloride using oxalyl chloride to afford (*R* or *S*)-**13**, which was then used without purification in the subsequent aromatic acylation. This

Scheme 1^a



^a (a) SOCl₂, C₅H₅N, CH₂Cl₂; (b) Br₂, ZnCl₂, AcOH; (c) Mg, EtMgBr, THF.

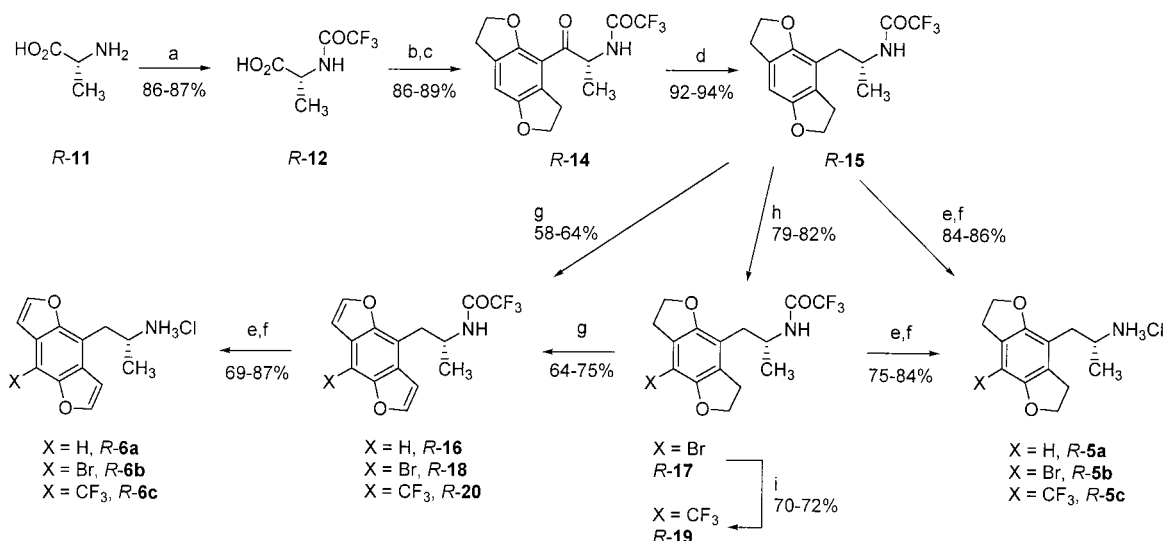
route afforded the optically pure ketone (*R* or *S*)-**14**, which was then reduced with triethylsilane in trifluoroacetic acid to afford the protected arylalkylamine (*R* or *S*)-**15**.¹³

The *N*-protected arylalkylamine (*R* or *S*)-**15** was hydrolyzed in base and then acidified to afford the hydrochloride salt of the unsubstituted product (*R* or *S*)-**5a**. The aromatic counterpart of this “non-*para*-substituted” amphetamine analogue was synthesized by oxidation of (*R* or *S*)-**15** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to produce the aromatized amide (*R* or *S*)-**16**.¹⁴ Subsequently, alkaline hydrolysis and acidification was used to obtain the hydrochloride salt of (*R* or *S*)-**6a**.

To complete the synthesis of the remaining compounds in this series, the amide (*R* or *S*)-**15** from above was brominated to afford the protected arylalkylamine (*R* or *S*)-**17**¹¹ followed by hydrolysis and conversion to the hydrochloride salt of (*R* or *S*)-**5b**. Compound (*R* or *S*)-**17** was likewise oxidized to the fully aromatic compound (*R* or *S*)-**18** using DDQ and then hydrolyzed and acidified to afford (*R* or *S*)-**6b** as the hydrochloride salt.

Brominated amide (*R* or *S*)-**17** was utilized to produce the final compounds (*R* or *S*)-**5c** and (*R* or *S*)-**6c**. The aromatic bromine of (*R* or *S*)-**17** was replaced by a trifluoromethyl substituent by reaction with copper iodide and tetramethylammonium trifluoroacetate¹⁵ to afford (*R* or *S*)-**19**, which was hydrolyzed and acidified to obtain the hydrochloride salt of (*R* or *S*)-**5c**. Finally, oxidation of (*R* or *S*)-**19** followed by hydrolysis and acidification of the product afforded the hydrochloride salt of (*R* or *S*)-**6c**. The Mosher amides¹⁶ of (*R*)- and (*S*)-**6c** were analyzed by HPLC to ascertain that no racemization had occurred during any of the synthetic steps; indeed this was found to be the case, with enantiomeric purities of both compounds in excess of 99%. In addition, it was noted that treatment of the tetrahydro compound (*R* or *S*)-**5b** with elemental bromine could under certain conditions lead to some oxidation to give small amounts of aromatized side products. In view of the high pharmacological activity that was found for (*R* or *S*)-**6b**, HPLC analysis of the *N*-trifluoroacetyl derivatives of (*R*)- and (*S*)-**5b** was used to verify that they contained no significant amounts of such oxidation products, which after hydrolysis might have contaminated (*R* or *S*)-**5b** and confounded the pharmacological results.

Scheme 2^a



^a (a) Et₃N, CF₃CO₂Et, MeOH; (b) (COCl)₂, CH₂Cl₂, C₅H₅N; (c) AlCl₃, **7**, CH₂Cl₂; (d) Et₃SiH, CF₃CO₂H; (e) NaOH, MeOH, H₂O; (f) HCl, EtOH (anhvd); (g) DDQ, dioxane; (h) Br₂, AcOH; (i) CF₃CO₂N(CH₃)₄, CuI, PhCH₃, DMF.

Table 1. Results of the Radioligand Competition Binding Studies of Nonrigid (series **4**) and Rigid (series **5** and **6**) Compounds at Cloned Rat 5-HT_{2A} and 5-HT_{2C} Receptors

compd	X	K_i , nM (SEM)	
		at 5-HT _{2A} , [³ H]DOB	at 5-HT _{2C} , [¹²⁵ I]DOI
(<i>R</i>)- 4a (2,5-DMA)	H	2340 (326)	520 (34)
(±)- 4b (DOB)	Br	2.2 (0.33)	2.8 (0.68)
(±)- 4c (DOTFM)	CF ₃	2.2 (0.26)	3.78 (1.12)
(<i>R</i>)- 5a	H	54.4 (5.40)	8.2 (2.4)
(<i>S</i>)- 5a	H	227 (24.5)	119 (31.8)
(<i>R</i>)- 5b	Br	1.2 (0.26)	0.26 (0.025)
(<i>S</i>)- 5b	Br	2.6 (0.33)	1.1 (0.20)
(<i>R</i>)- 5c	CF ₃	0.70 (0.090)	1.9 (0.32)
(<i>S</i>)- 5c	CF ₃	2.0 (0.17)	1.6 (0.19)
(<i>R</i>)- 6a	H	1.5 (0.090)	0.79 (0.24)
(<i>S</i>)- 6a	H	37.9 (5.40)	6.0 (0.17)
(<i>R</i>)- 6b	Br	0.31 (0.042)	0.11 (0.014)
(<i>S</i>)- 6b	Br	0.69 (0.083)	0.25 (0.046)
(<i>R</i>)- 6c	CF ₃	0.29 (0.030)	0.40 (0.13)
(<i>S</i>)- 6c	CF ₃	0.32 (0.030)	0.69 (0.098)

Pharmacology

Radioligand binding assays and phosphoinositide hydrolysis were employed to pharmacologically characterize this class of 5-HT_{2A/2C} receptor agonists. As indicated in Table 1, the 5-HT_{2A} and 5-HT_{2C} receptor competition binding data were generated using [³H]-DOB and [¹²⁵I]DOI, respectively. As a measure of functional activity, compounds were analyzed for their ability to stimulate phosphoinositide hydrolysis in NIH-3T3 cells expressing the 5-HT_{2A} receptor. The results of those assays are shown in Table 2.

Results and Discussion

The pharmacological data generated by the testing of these enantiomerically pure, rigid analogues have led to some new ideas about the interactions of the 5-HT_{2A} receptor binding site with agonist ligands. Perhaps the most interesting finding in Table 1 is that affinity for both of the 5-HT₂ receptor isoforms is generally increased in the rigidified tetrahydrobenzo[1,2-*b*;4,5-*b'*]-difuran compounds (series 5) compared to their corresponding 2,5-dimethoxyamphetamine analogues (series

Table 2. Results of the Phosphoinositide Hydrolysis Studies of Nonrigid (series **4**) and Rigid (series **5** and **6**) Compounds at Cloned Rat 5-HT_{2A} Receptors

compd	X	EC ₅₀ at 5-HT _{2A} , nM (SEM)	percent maximal 5-HT stimulation (SEM)
(R)- 4a (2,5-DMA)	H	> 10000	16 (3.1) @ 100 μ M
(\pm)- 4b (DOB)	Br	72 (3.6)	79 (6.0)
(\pm)- 4c (DOTFM)	CF ₃	68.4 (12.6)	86 (3.5)
(R)- 5a	H	5650 (376)	99 (0.7)
(S)- 5a	H	2360 (210)	62 (3.1)
(R)- 5b	Br	8.38 (1.86)	80 (7.8)
(S)- 5b	Br	35 (1.0)	76 (5.0)
(R)- 5c	CF ₃	28 (6.7)	69 (3.9)
(S)- 5c	CF ₃	30 (6.2)	60 (1.2)
(R)- 6a	H	590 (20)	76 (3.2)
(S)- 6a	H	650 (68)	68 (2.3)
(R)- 6b	Br	2.7 (0.55)	93 (9.9)
(S)- 6b	Br	19 (1.6)	79 (1.5)
(R)- 6c	CF ₃	3.8 (0.53)	60 (3.9)
(S)- 6c	CF ₃	12 (1.4)	52 (6.0)

4). A similar potency trend is observed in the phosphoinositide hydrolysis data (Table 2). One reasonable explanation for this phenomenon is that the tethered alkyl ether groups of the two rigid series are acting as conformationally restricted mimics of the methoxy substituents in the analogous amphetamine analogues (series 4). In this view, the conformationally restricted compounds have higher affinity because they do not incur the entropic penalty experienced when the compounds with freely rotating methoxy groups bind. Another possible explanation for the increase in binding affinity for the benzo[1,2-*b*:4,5-*b'*]difuran analogues is that the alkylamine side chain of these analogues is likely to exist in an anti-periplanar conformation (in a plane perpendicular to that of the aromatic system). Solution NMR studies of amphetamine analogues indicate that the alkylamine side chain resides in this out-of-plane orientation under simulated physiological conditions.¹⁷ If the out-of-plane rotamer is the biologically active conformation, then these rigid analogues may also derive increased affinity through the enhancement of energetic accessibility to the anti-periplanar conformation.

An additional trend that can be observed in Tables 1 and 2 is that the benzo[1,2-*b*:4,5-*b'*]difuran-containing compounds (series **6**) bind with higher affinity and exhibit increased potency relative to the corresponding tetrahydrobenzo[1,2-*b*:4,5-*b'*]difurans (series **5**), indicating that the compounds in series **6** possess more favorable interactions with the agonist binding site. This may be due to the increased hydrophobicity of the extended tricyclic aromatic nucleus in **6a–c** relative to the tetrahydro congeners **5a–c** and a resulting greater tendency to partition into the hydrophobic receptor binding site. It is also possible that the extended aromaticity of the benzo[1,2-*b*:4,5-*b'*]difurans (series **6**) may result in enhanced affinity by increasing the effective aromatic surface area on the ligand available for favorable π -stacking interactions with the agonist binding site, while still maintaining some (albeit weaker) hydrogen-bond acceptor properties of the furan oxygen atoms. It is interesting to note that although potency is generally increased for the aromatic compounds **6a–c** relative to the tetrahydro compounds **5a–c**, the intrinsic activity of these compounds remains largely unchanged.

The data in Tables 1 and 2 indicate that (with the exception of the 5-HT_{2C} data for (*R*)- and (*S*)-**5c**) the *R*-enantiomer binds with higher affinity and exhibits greater potency than the corresponding *S*-antipode. However, the data also indicate that the degree of enantioselectivity exhibited by the pairs of enantiomers in the two rigid series is relatively modest, *except for the compounds lacking a substituent para to the side chain, i.e., 5a and 6a*. It might be inferred that a hydrophobic substituent at that location induces a conformational change in the ligand-binding domain such that the region in the vicinity of the α -methyl group is dramatically altered. It is known that the effect of appending a hydrophobic substituent to the 4-position of amphetamine analogues is to increase hallucinogenic activity, presumably by increasing affinity and/or efficacy at the 5-HT_{2A} receptor.¹⁸ This effect is dramatically demonstrated in this new series of arylalkylamine analogues in progressing from (*R* or *S*)-**5a** to the brominated arylalkylamine (*R*- or *S*)-**5b**. Only affinity is increased slightly when comparing (*R* or *S*)-**5b** to the trifluoromethylated arylalkylamine (*R* or *S*)-**5c**.

Nevertheless, it must be noted that the nonsubstituted (*R*)-**6a** has rather remarkable affinity, being about comparable to the most potent amphetamine derivatives such as **4c**, although its functional potency is still rather low (EC₅₀ ca. 600 nM). Therefore, the fully aromatic system must compensate in some way for the lack of this substituent, even though its absence is clearly relevant to the high degree of stereoselectivity observed in **6a** versus **6b**. These will be interesting effects to study when a satisfactory three-dimensional model of the 5-HT_{2A} receptor is ultimately developed.

In summary, tethering the 2,5-dimethoxy substituents of hallucinogenic amphetamines in the form of tetrahydrofuran or furan rings has led to the most potent 5-HT_{2A/2C} receptor ligands yet reported. Our anticipation that receptor isoform selectivity might arise in these series has not been borne out, but these compounds will be useful tools in further exploring the role of these receptors in behavior and cognition.

Experimental Section

Chemistry. All reagents were commercially available and were used without further purification unless otherwise indicated. Dry THF and diethyl ether were obtained by distillation from benzophenone-sodium under nitrogen immediately before use. Melting points were determined using a Thomas-Hoover apparatus and are uncorrected. ¹H NMR spectra were recorded using a 300-MHz Bruker ARX-300 NMR spectrometer. Chemical shifts are reported in δ values ppm relative to an internal reference (0.03%, v/v) of tetramethylsilane (TMS) in CDCl₃, except where noted. Chemical ionization mass spectra (CIMS) using isobutane as the carrier gas were obtained with a Finnigan 4000 spectrometer. Elemental analyses were performed by the Purdue University Microanalysis Laboratory and are within $\pm 0.4\%$ of the calculated values unless otherwise noted. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at the sodium D-line (λ = 589 nm). Thin-layer chromatography was performed using J.T. Baker flex silica gel IB2-F, plastic-backed sheets with fluorescent indicator, visualizing with UV light at 254 nm and eluting with 4:1 hexanes–ethyl acetate unless otherwise noted. Column chromatography was carried out using silica gel 60, 230–400 mesh (J.T. Baker). All reactions were carried out under an inert atmosphere of argon unless otherwise indicated.

1,4-Bis(2-chloroethoxy)benzene (9).¹⁹ Pyridine (29.4 mL, 364 mmol) was added to a mechanically stirred solution of 1,4-bis(hydroxyethoxy)benzene (**8**) (Aldrich; 30.0 g, 152 mmol) in CH₂Cl₂ (300 mL) at 0 °C. Next, thionyl chloride (25.4 mL, 348 mmol) was added dropwise such that the internal temperature did not exceed 5 °C.²⁰ This mixture was allowed to warm gradually to room temperature and was stirred overnight. Aqueous 2 N HCl (500 mL) was added slowly and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 \times 75 mL) and the organic extracts were combined. The pooled organic extracts were then washed with aqueous 2 N HCl (2 \times 200 mL), water (200 mL), 1 N NaOH (100 mL), and brine (100 mL). The organic extracts were then dried (MgSO₄), filtered, and evaporated to leave a tan solid that was recrystallized from ethanol to afford white crystals: 31.4 g, 88%; mp 90–91 °C; ¹H NMR (CDCl₃) δ 3.79 (t, 4 H, ArOCH₂CH₂Cl, *J* = 6.0 Hz), 4.19 (t, 4 H, ArOCH₂CH₂Cl, *J* = 6.0 Hz), 6.87 (s, 4 H, *ArH*); CIMS *m/z* 235 (*M* + *H*⁺).

1,4-Bis(2-chloroethoxy)-2,5-dibromobenzene (10).¹¹ Zinc chloride (38.2 g, 280 mmol) was added to a solution of **9** (27.5 g, 117 mmol) in acetic acid (280 mL). After enclosing the apparatus in aluminum foil to exclude light, bromine (39.3 g, 246 mmol) dissolved in acetic acid (55 mL) was added dropwise to the suspension over 1.5 h. The reaction was allowed to stir overnight, during which time a precipitate had formed. The reaction was diluted with aqueous saturated sodium thiosulfate (500 mL) and extracted with CH₂Cl₂ (5 \times 200 mL). The organic layers were combined and washed with aqueous 1 N NaOH (1 \times 200 mL), brine (100 mL), dried (MgSO₄), filtered, and evaporated to leave an off-white solid. Recrystallization from ethanol afforded a crystalline white product: 50.0 g, 91%; mp 120 °C (lit.¹¹ mp 119 °C); ¹H NMR (CDCl₃) δ 3.83 (t, 4 H, ArOCH₂CH₂Cl, *J* = 6.3 Hz), 4.23 (t, 4 H, ArOCH₂CH₂Cl, *J* = 6.3 Hz), 7.14 (s, 2 H, *ArH*); CIMS *m/z* 391 (*M* + *H*⁺).

2,3,6,7-Tetrahydrobenzo[1,2-*b*:4,5-*b'*]difuran (7).¹⁰ To a suspension of magnesium powder (Aldrich, –50 mesh, 99+%; 3.7 g, 152 mmol) in anhydrous THF (50 mL) was slowly added EtMgBr (3.4 mL, 10 mmol, 3 M solution in Et₂O).²¹ An anhydrous THF solution (125 mL) of the dibrominated compound **10** (20.0 g, 51.0 mmol) was then added dropwise such that the internal reaction temperature did not exceed 35 °C. Upon completion of the addition, the reaction was heated at reflux for 3 h. The reaction was then cooled to room temperature and carefully poured into cold 1 N HCl (200 mL). Upon cessation of gas evolution, the mixture was extracted with Et₂O (3 \times 300 mL). The organic layers were combined and washed with aqueous 1 N NaOH (4 \times 75 mL), brine (50 mL), dried (MgSO₄), filtered, and concentrated by rotary evaporation to afford a tan solid. This was recrystallized from ethanol to afford off-white, platelike crystals: 6.5 g, 79%; mp 155 °C (lit.¹¹

mp 155–156 °C); ¹H NMR (CDCl₃) δ 3.13 (t, 4 H, ArOCH₂CH₂, *J* = 8.5 Hz), 4.52 (t, 4 H, ArOCH₂CH₂, *J* = 8.5 Hz), 6.63 (s, 2 H, ArH); CIMS *m/z* 163 (M + H⁺).

(*R*)-*N*-Trifluoroacetylalanine ((*R*)-12).¹² The procedure of Curphey was followed exactly except for a slight modification of the acidic workup. Triethylamine (3.1 mL, 22 mmol) was added to a solution of D-alanine ((*R*)-11; 99%) (2.0 g, 22 mmol) in MeOH (11 mL). After 5 min, ethyl trifluoroacetate (3.3 mL, 28 mmol) was added and the reaction was allowed to stir for 24 h. The solvent was removed by rotary evaporation and the residue that remained was dissolved in H₂O (35 mL) and acidified with concentrated HCl (4 mL). After stirring for 15 min, the mixture was extracted with ethyl acetate (4 × 30 mL) and the organic layers were combined and washed with brine (25 mL), dried (MgSO₄), filtered, and concentrated by rotary evaporation to leave a clear oil. After being subjected to high vacuum for 24 h, the clear oil solidified into a fluffy, hygroscopic solid: 2.7 g, 86%; mp 69 °C (lit.¹² mp 70–71 °C); ¹H NMR (CDCl₃) δ 1.58 (d, 3 H, CHCH₃, *J* = 7.5 Hz), 4.68 (p, 1 H, CHCH₃, *J* = 7.5 Hz), 6.87 (bs, 1 H, NH).

(*S*)-*N*-Trifluoroacetylalanine ((*S*)-12).¹² The title compound was prepared from L-alanine ((*S*)-11; 99%) as described for compound (*R*)-12: 87%; mp 70 °C (lit.¹² mp 70–71 °C); ¹H NMR (CDCl₃) δ 1.58 (d, 3 H, CHCH₃, *J* = 7.5 Hz), 4.68 (p, 1 H, CHCH₃, *J* = 7.5 Hz), 6.87 (bs, 1 H, NH).

(*R*)-(+)-*N*-Trifluoroacetyl-2,3,6,7-tetrahydro-4-alanylbenzo[1,2-*b*:4,5-*b'*]difuran ((*R*)-14). Trifluoroacetamide-protected D-alanine ((*R*)-12) (4.09 g, 22 mmol) was added to a pre-tared flask and placed under high vacuum for 24 h to remove any residual moisture. The flask was then reweighed to record an accurate weight of the starting material. Next, CH₂Cl₂ (100 mL) was added to the flask, followed by pyridine (2 drops) and the solution was cooled to 0 °C. Oxalyl chloride (4.3 mL, 49 mmol) was then added via syringe and the reaction was allowed to gradually warm to room temperature and stir for 3.5 h. The solvent and excess oxalyl chloride were removed by rotary evaporation at 35 °C to afford acid chloride (*R*)-13, which was not characterized. The heterocycle **7** (1.1 g, 6.6 mmol) was dissolved in CH₂Cl₂ (35 mL) and this solution was added slowly via dropping funnel to a suspension of AlCl₃ (2.4 g, 18.3 mmol) in CH₂Cl₂ (50 mL). This was followed by slow addition of the acid chloride (*R*)-13 dissolved in CH₂Cl₂ (45 mL). The mixture was allowed to stir for 16 h, at which time TLC showed only one yellow spot. The reaction mixture was poured slowly onto ice to quench the reaction and the two phases were then separated. The aqueous layer was extracted with CH₂Cl₂ (4 × 75 mL) and the organic layers were combined and washed with cold, aqueous 1 N HCl (75 mL), H₂O (50 mL), and then saturated NaHCO₃ (2 × 50 mL). The organic solution was then dried (MgSO₄), filtered, and concentrated to leave a yellow solid that was recrystallized from methanol to afford fluffy, yellow crystals: 1.88 g, 86%; mp 209–210 °C; ¹H NMR (CDCl₃) δ 1.46 (d, 3 H, CHCH₃, *J* = 6.8 Hz), 3.21 (m, 2 H, ArOCH₂CH₂), 3.33 (p, 1 H, ArOCH₂CH₂, *J* = 8.5 Hz), 3.61 (p, 1 H, ArOCH₂CH₂, *J* = 9.0 Hz), 4.64 (m, 4 H, ArOCH₂CH₂), 5.62 (p, 1 H, CHCH₃, *J* = 6.8 Hz), 6.90 (s, 1 H, ArH), 7.64 (bs, 1 H, NH); [α]_D = +56.0° (*c* = 0.01, CH₃CN); CIMS *m/z* 330 (M + H⁺). Anal. (C₁₅H₁₄F₃NO₄) C, H, N.

(*S*)-(-)-*N*-Trifluoroacetyl-2,3,6,7-tetrahydro-4-alanylbenzo[1,2-*b*:4,5-*b'*]difuran ((*S*)-14). The title compound was prepared from (*S*)-12 as described for compound (*R*)-14: 89%; mp 210–211 °C; ¹H NMR (CDCl₃) δ 1.46 (d, 3 H, CHCH₃, *J* = 6.8 Hz), 3.21 (m, 2 H, ArOCH₂CH₂), 3.33 (p, 1 H, ArOCH₂CH₂, *J* = 8.5 Hz), 3.61 (p, 1 H, ArOCH₂CH₂, *J* = 9.0 Hz), 4.64 (m, 4 H, ArOCH₂CH₂), 5.62 (p, 1 H, CHCH₃, *J* = 6.8 Hz), 6.90 (s, 1 H, ArH), 7.64 (bs, 1 H, NH); [α]_D = -56.1° (*c* = 0.01, CH₃CN); CIMS *m/z* 330 (M + H⁺). Anal. (C₁₅H₁₄F₃NO₄) C, H, N.

(*R*)-(+)-*N*-Trifluoroacetyl-1-(2,3,6,7-tetrahydrobenzo[1,2-*b*:4,5-*b'*]difuran-4-yl)-2-aminopropane ((*R*)-15). Ketone (*R*)-14 (0.94 g, 2.9 mmol) was dissolved in trifluoroacetic acid (9.4 mL) and then triethylsilane (2.3 mL, 14.5 mmol) was added. The mixture was heated at reflux for 6 h, at which time TLC showed no starting material. The reaction was cooled to room temperature followed by the very slow addition of

saturated, aqueous NaHCO₃ solution until evolution of gas had ceased and the solution remained alkaline. The mixture was then extracted with Et₂O (4 × 75 mL), the organic layers combined and dried (MgSO₄), filtered and evaporated to leave a tan solid. The product was triturated with hexanes and the resulting suspension was then vacuum filtered to leave a white solid: 0.84 g, 92%; mp 139–140 °C; ¹H NMR (CDCl₃) δ 1.27 (d, 3 H, CHCH₃, *J* = 6.6 Hz), 2.75 (d, 2 H, ArCH₂CH, *J* = 6.0 Hz), 3.09 (t, 2 H, ArOCH₂CH₂, *J* = 8.6 Hz), 3.17 (t, 2 H, ArOCH₂CH₂, *J* = 8.7 Hz), 4.16 (p, 1 H, ArCH₂CH, *J* = 6.5 Hz), 4.54 (t, 2 H, ArOCH₂CH₂, *J* = 8.4 Hz), 4.56 (t, 2 H, ArOCH₂CH₂), 6.56 (s, 1 H, ArH), 7.73 (bs, 1 H, NH); [α]_D = +8.80° (*c* = 0.081, CH₃CN); CIMS *m/z* 316 (M + H⁺). Anal. (C₁₅H₁₆F₃NO₃) C, H, N.

(*S*)-(-)-*N*-Trifluoroacetyl-1-(2,3,6,7-tetrahydrobenzo[1,2-*b*:4,5-*b'*]difuran-4-yl)-2-aminopropane ((*S*)-15). The title compound was prepared from (*S*)-14 as described for compound (*R*)-15: 94%; mp 139–140 °C; ¹H NMR (CDCl₃) δ 1.27 (d, 3 H, CHCH₃, *J* = 6.6 Hz), 2.75 (d, 2 H, ArCH₂CH, *J* = 6.0 Hz), 3.09 (t, 2 H, ArOCH₂CH₂, *J* = 8.6 Hz), 3.17 (t, 2 H, ArOCH₂CH₂, *J* = 8.7 Hz), 4.16 (p, 1 H, ArCH₂CH, *J* = 6.5 Hz), 4.54 (t, 2 H, ArOCH₂CH₂, *J* = 8.4 Hz), 4.56 (t, 2 H, ArOCH₂CH₂), 6.56 (s, 1 H, ArH), 7.73 (bs, 1 H, NH); [α]_D = -8.76° (*c* = 0.069, CH₃CN); CIMS *m/z* 316 (M + H⁺). Anal. (C₁₅H₁₆F₃NO₃) C, H, N.

Representative Procedure for Hydrolysis of Trifluoroacetamides: (*R*)-(-)-1-(2,3,6,7-Tetrahydrobenzo[1,2-*b*:4,5-*b'*]difuran-4-yl)-2-aminopropane Hydrochloride ((*R*)-5a·HCl). The protected amine (*R*)-15 (0.1 g, 0.3 mmol) was dissolved in MeOH (20 mL) and cooled to 0 °C. Aqueous 5 N NaOH (5 mL) was added to this solution and the mixture was allowed to stir overnight and was then diluted with Et₂O (50 mL). The phases were separated and the aqueous layer was extracted with Et₂O (3 × 15 mL). The organic layers were combined, dried (MgSO₄), filtered and evaporated to yield a tan oil. This oil was taken up in anhydrous Et₂O (15 mL) and filtered through glass wool. A slight excess of ethanolic 1 N HCl was added dropwise to the solution with vigorous stirring. The flask was then placed in a freezer overnight and the precipitate was collected by vacuum filtration. The resulting solid was recrystallized from *i*-PrOH to afford white, fluffy crystals: 0.073 g, 86%; mp 275–276 °C dec; ¹H NMR (D₂O) δ 1.28 (d, 3 H, CHCH₃, *J* = 6.9 Hz), 2.83 (d, 2 H, ArCH₂CH, *J* = 6.9 Hz), 3.13 (dt, 4 H, ArOCH₂CH₂, *J* = 7.8 Hz), 3.66 (m, 1 H, ArCH₂CH, *J* = 6.9 Hz), 4.55 (dt, 4 H, ArOCH₂CH₂, *J* = 9.0 Hz), 6.68 (s, 1 H, ArH); [α]_D = -11.78° (*c* = 0.011, DMF); CIMS *m/z* 220 (M + H⁺). Anal. (C₁₃H₁₈ClNO₂) C, H, N.

(*S*)-(+)-1-(2,3,6,7-Tetrahydrobenzo[1,2-*b*:4,5-*b'*]difuran-4-yl)-2-aminopropane Hydrochloride ((*S*)-5a·HCl). The title compound was prepared from (*S*)-15 as described for (*R*)-5a·HCl: 84%; mp 275–276 °C dec; ¹H NMR (D₂O) δ 1.28 (d, 3 H, CHCH₃, *J* = 6.9 Hz), 2.83 (d, 2 H, ArCH₂CH, *J* = 6.9 Hz), 3.13 (dt, 4 H, ArOCH₂CH₂, *J* = 7.8 Hz), 3.66 (m, 1 H, ArCH₂CH, *J* = 6.9 Hz), 4.55 (dt, 4 H, ArOCH₂CH₂, *J* = 9.0 Hz), 6.68 (s, 1 H, ArH); [α]_D = +11.72° (*c* = 0.011, DMF); CIMS *m/z* 220 (M + H⁺). Anal. (C₁₃H₁₈ClNO₂) C, H, N.

Representative Procedure for Aromatization of Substituted 2,3,6,7-Tetrahydrobenzo[1,2-*b*:4,5-*b'*]difurans to Benzo[1,2-*b*:4,5-*b'*]difurans: (*R*)-(+)-*N*-Trifluoroacetyl-1-(benzo[1,2-*b*:4,5-*b'*]difuran-4-yl)-2-aminopropane ((*R*)-16). A solution of DDQ (0.42 g, 1.85 mmol) in dioxane (8 mL) was slowly added to a solution of protected amine (*R*)-15 (0.20 g, 0.63 mmol) in dioxane (10 mL).¹⁴ The solution was heated at reflux for 24 h, at which time TLC indicated reaction completion. The reaction was then cooled to room temperature and the precipitate that formed was removed by vacuum filtration. The filter cake was washed thoroughly with CH₂Cl₂ and then the solvents were removed by rotary evaporation. The brown oil that remained was subjected to column chromatography (4:1 hexanes–ethyl acetate as eluent) to afford a white solid product: 0.134 g, 64%; mp 150–151 °C; ¹H NMR (CDCl₃) δ 1.29 (d, 3 H, CHCH₃, *J* = 6.6 Hz), 3.38 (dd, 2 H, ArCH₂CH, *J* = 6.0, 3.0 Hz), 4.48 (m, 1 H, ArCH₂CH, *J* = 6.9 Hz), 6.54 (bs, 1 H, NH), 6.85 (d, 1 H, ArH, *J* = 2.4 Hz), 6.90 (d, 1 H, ArH, *J*

= 2.4 Hz), 7.58 (s, 1 H, ArH), 7.64 (d, 1 H, ArH, J = 2.4 Hz), 7.67 (d, 1 H, ArH, J = 2.1 Hz); $[\alpha]_D$ = +3.06° (c = 0.006, CH₃CN); CIMS m/z 312 (M + H^+). Anal. (C₁₅H₁₂F₃NO₂) C, H, N.

(S)-(-)-N-Trifluoroacetyl-1-(benzo[1,2-*b*:4,5-*b'*]difuran-4-yl)-2-aminopropane ((S)-16). The title compound was prepared from (S)-15 by the general procedure described for compound (R)-16: 58%; mp 152–153 °C; ¹H NMR (CDCl₃) δ 1.29 (d, 3 H, CHCH₃, J = 6.6 Hz), 3.38 (dd, 2 H, ArCH₂CH, J = 6.0, 3.0 Hz), 4.48 (m, 1 H, ArCH₂CH, J = 6.9 Hz), 6.54 (bs, 1 H, NH), 6.85 (d, 1 H, ArH, J = 2.4 Hz), 6.90 (d, 1 H, ArH, J = 2.4 Hz), 7.58 (s, 1 H, ArH), 7.64 (d, 1 H, ArH, J = 2.4 Hz), 7.67 (d, 1 H, ArH, J = 2.1 Hz); $[\alpha]_D$ = -3.04° (c = 0.006, CH₃CN); CIMS m/z 312 (M + H^+). Anal. (C₁₅H₁₂F₃NO₂) C, H, N.

(R)-(-)-1-(Benzo[1,2-*b*:4,5-*b'*]difuran-4-yl)-2-aminopropane Hydrochloride ((R)-6a·HCl). The title compound was prepared from (R)-16 by the general procedure described for compound (R)-5a·HCl: 81%; mp 269 °C dec; ¹H NMR (D₂O) δ 1.29 (d, 3 H, CHCH₃, J = 6.9 Hz), 3.36 (d, 2 H, ArCH₂CH, J = 6.9 Hz), 3.85 (m, 1 H, ArCH₂CH, J = 6.9 Hz), 6.94 (d, 1 H, ArH, J = 1.2 Hz), 6.98 (d, 1 H, ArH, J = 1.2 Hz), 7.64 (s, 1 H, ArH), 7.77 (s, 1 H, ArH), 7.78 (s, 1 H, ArH); $[\alpha]_D$ = -9.54° (c = 0.0102, DMF); CIMS m/z 216 (M + H^+). Anal. (C₁₃H₁₄ClNO₂) C, H, N.

(S)-(+)-1-(Benzo[1,2-*b*:4,5-*b'*]difuran-4-yl)-2-aminopropane Hydrochloride ((S)-6a·HCl). The title compound was prepared from (S)-16 by the general procedure described for compound (R)-5a·HCl: 82%; mp 270 °C dec; ¹H NMR (D₂O) δ 1.29 (d, 3 H, CHCH₃, J = 6.9 Hz), 3.36 (d, 2 H, ArCH₂CH, J = 6.9 Hz), 3.85 (m, 1 H, ArCH₂CH, J = 6.9 Hz), 6.94 (d, 1 H, ArH, J = 1.2 Hz), 6.98 (d, 1 H, ArH, J = 1.2 Hz), 7.64 (s, 1 H, ArH), 7.77 (s, 1 H, ArH), 7.78 (s, 1 H, ArH); $[\alpha]_D$ = +9.58° (c = 0.0102, DMF); CIMS m/z 216 (M + H^+). Anal. (C₁₃H₁₄ClNO₂) C, H, N.

(R)-(+)-N-Trifluoroacetyl-1-(8-bromo-2,3,6,7-tetrahydrobenzo[1,2-*b*:4,5-*b'*]difuran-4-yl)-2-aminopropane ((R)-17). The protected amine (R)-15 (1.1 g, 3.5 mmol) was dissolved in acetic acid (70 mL) and the flask was covered with aluminum foil to exclude light.¹¹ This solution was cooled to 15 °C and a solution of bromine (0.54 g, 3.5 mmol) in acetic acid (12 mL) was added dropwise. The reaction was allowed to warm to room temperature and stir for 4.5 h, at which time a precipitate had formed and TLC indicated the absence of starting material. The reaction was quenched by the addition of H₂O (100 mL) and extracted with CH₂Cl₂ (5 × 50 mL). The organic layers were combined, dried (MgSO₄), filtered, and evaporated to afford 1.0 g (79%) of the product as a white solid. Care should be taken to use not more than 1.0 equivalent of bromine in this procedure and to recrystallize the product if any impurities are observed, since we have noted that bromine can oxidize the dihydrofuran moieties to furans under some circumstances. An analytical sample was recrystallized from ethyl acetate–hexane: mp 201–202 °C; ¹H NMR (CDCl₃) δ 1.27 (d, 3 H, CHCH₃, J = 6.3 Hz), 2.71 (dd, 2 H, ArCH₂CH, J = 7.2, 1.5 Hz), 3.20 (t, 4 H, ArOCH₂CH₂, J = 8.7 Hz), 4.13 (p, 1 H, ArCH₂CH, J = 6.6 Hz), 4.59 (t, 2 H, ArOCH₂CH₂, J = 8.4 Hz), 4.65 (t, 2 H, ArOCH₂CH₂, J = 8.4 Hz), 7.47 (bs, 1 H, NH); $[\alpha]_D$ = +6.6° (c = 0.00445, CH₃CN); CIMS m/z 394 (M + H^+). Anal. (C₁₅H₁₅BrF₃NO₂) C, H, N.

(S)-(-)-N-Trifluoroacetyl-1-(8-bromo-2,3,6,7-tetrahydrobenzo[1,2-*b*:4,5-*b'*]difuran-4-yl)-2-aminopropane ((S)-17). The title compound was prepared from (S)-15 by the general procedure described for compound (R)-17: 82%; mp 201–202 °C; ¹H NMR (CDCl₃) δ 1.27 (d, 3 H, CHCH₃, J = 6.3 Hz), 2.71 (dd, 2 H, ArCH₂CH, J = 7.2, 1.5 Hz), 3.20 (t, 4 H, ArOCH₂CH₂, J = 8.7 Hz), 4.13 (p, 1 H, ArCH₂CH, J = 6.6 Hz), 4.59 (t, 2 H, ArOCH₂CH₂, J = 8.4 Hz), 4.65 (t, 2 H, ArOCH₂CH₂, J = 8.4 Hz), 7.47 (bs, 1 H, NH); $[\alpha]_D$ = -6.9° (c = 0.00445, CH₃CN); CIMS m/z 394 (M + H^+). Anal. (C₁₅H₁₅BrF₃NO₂) C, H, N.

(R)-(-)-1-(8-Bromo-2,3,6,7-tetrahydrobenzo[1,2-*b*:4,5-*b'*]difuran-4-yl)-2-aminopropane Hydrochloride ((R)-5b·HCl). The title compound was prepared from (R)-17 by the general procedure described for compound (R)-5a·HCl: 75%; mp 282–283 °C; ¹H NMR (D₂O) δ 1.27 (d, 3 H, CHCH₃, J =

6.3 Hz), 2.78 (dd, 2 H, ArCH₂CH, J = 7.2, 3.3 Hz), 3.14 (t, 2 H, ArOCH₂CH₂, J = 8.7 Hz), 3.23 (t, 2 H, ArOCH₂CH₂, J = 8.7 Hz), 3.63 (m, 1 H, ArCH₂CH, J = 6.9 Hz), 4.61 (q, 4 H, ArOCH₂CH₂, J = 8.7 Hz); $[\alpha]_D$ = -10.82° (c = 0.0089, DMF); CIMS m/z 297 (M + H^+). Anal. (C₁₃H₁₇BrClNO₂) C, H, N.

(S)-(+)-1-(8-Bromo-2,3,6,7-tetrahydrobenzo[1,2-*b*:4,5-*b'*]difuran-4-yl)-2-aminopropane Hydrochloride ((S)-5b·HCl). The title compound was prepared from (S)-17 by the general procedure described for compound (R)-5a·HCl: 78%; mp 282–283 °C; ¹H NMR (D₂O) δ 1.27 (d, 3 H, CHCH₃, J = 6.3 Hz), 2.78 (dd, 2 H, ArCH₂CH, J = 7.2, 3.3 Hz), 3.14 (t, 2 H, ArOCH₂CH₂, J = 8.7 Hz), 3.23 (t, 2 H, ArOCH₂CH₂, J = 8.7 Hz), 3.63 (m, 1 H, ArCH₂CH, J = 6.9 Hz), 4.61 (q, 4 H, ArOCH₂CH₂, J = 8.7 Hz); $[\alpha]_D$ = +10.80° (c = 0.0089, DMF); CIMS m/z 297 (M + H^+). Anal. (C₁₃H₁₇BrClNO₂) C, H, N.

(R)-(+)-N-Trifluoroacetyl-1-(8-bromobenzo[1,2-*b*:4,5-*b'*]difuran-4-yl)-2-aminopropane ((R)-18). The title compound was prepared from (R)-17 by the general procedure described for compound (R)-16: 68%; mp 215–216 °C; ¹H NMR (CDCl₃) δ 1.26 (d, 3 H, CHCH₃, J = 6.7 Hz), 3.35 (dd, 2 H, ArCH₂CH, J = 6.4, 3.3 Hz), 4.46 (m, 1 H, ArCH₂CH, J = 6.8 Hz), 6.41 (bs, 1 H, NH), 6.92 (d, 1 H, ArH, J = 2.2 Hz), 6.99 (d, 1 H, ArH, J = 2.2 Hz), 7.69 (d, 1 H, ArH, J = 2.2 Hz), 7.73 (d, 1 H, ArH, J = 2.3 Hz); $[\alpha]_D$ = +17.7° (c = 0.0075, CH₃CN); CIMS m/z 390 (M + H^+). Anal. (C₁₅H₁₁BrF₃NO₂) C, H, N.

(S)-(-)-N-Trifluoroacetyl-1-(8-bromobenzo[1,2-*b*:4,5-*b'*]difuran-4-yl)-2-aminopropane ((S)-18). The title compound was prepared from (S)-17 by the general procedure described for compound (R)-16: 64%; mp 214–215 °C; ¹H NMR (CDCl₃) δ 1.26 (d, 3 H, CHCH₃, J = 6.7 Hz), 3.35 (dd, 2 H, ArCH₂CH, J = 6.4, 3.3 Hz), 4.46 (m, 1 H, ArCH₂CH, J = 6.8 Hz), 6.41 (bs, 1 H, NH), 6.92 (d, 1 H, ArH, J = 2.2 Hz), 6.99 (d, 1 H, ArH, J = 2.2 Hz), 7.69 (d, 1 H, ArH, J = 2.2 Hz), 7.73 (d, 1 H, ArH, J = 2.3 Hz); $[\alpha]_D$ = -17.2° (c = 0.0075, CH₃CN); CIMS m/z 390 (M + H^+). Anal. (C₁₅H₁₁BrF₃NO₂) C, H, N.

(R)-(-)-1-(8-Bromobenzo[1,2-*b*:4,5-*b'*]difuran-4-yl)-2-aminopropane Hydrochloride ((R)-6b·HCl). The title compound was prepared from (R)-18 by the general procedure described for compound (R)-5a·HCl: 87%; mp 290 °C dec; ¹H NMR (D₂O) δ 1.23 (d, 3 H, CHCH₃, J = 6.6 Hz), 3.21 (d, 2 H, ArCH₂CH, J = 6.9 Hz), 3.74 (m, 1 H, ArCH₂CH, J = 6.9 Hz), 6.84 (d, 1 H, ArH, J = 2.1 Hz), 6.96 (d, 1 H, ArH, J = 2.4 Hz), 7.73 (d, 1 H, ArH, J = 2.4 Hz), 7.76 (s, 1 H, ArH, J = 2.4 Hz); $[\alpha]_D$ = -20.1° (c = 0.005, DMF); CIMS m/z 294 (M + H^+). Anal. (C₁₃H₁₃BrClNO₂) C, H, N.

(S)-(+)-1-(8-Bromobenzo[1,2-*b*:4,5-*b'*]difuran-4-yl)-2-aminopropane Hydrochloride ((S)-6b·HCl). The title compound was prepared from (S)-18 by the general procedure described for compound (R)-5a·HCl: 85%; mp 291 °C dec; ¹H NMR (D₂O) δ 1.23 (d, 3 H, CHCH₃, J = 6.6 Hz), 3.21 (d, 2 H, ArCH₂CH, J = 6.9 Hz), 3.74 (m, 1 H, ArCH₂CH, J = 6.9 Hz), 6.84 (d, 1 H, ArH, J = 2.1 Hz), 6.96 (d, 1 H, ArH, J = 2.4 Hz), 7.73 (d, 1 H, ArH, J = 2.4 Hz), 7.76 (s, 1 H, ArH, J = 2.4 Hz); $[\alpha]_D$ = +20.8° (c = 0.005, DMF); CIMS m/z 294 (M + H^+). Anal. (C₁₃H₁₃BrClNO₂) C, H, N.

(R)-(+)-N-Trifluoroacetyl-1-(8-trifluoromethyl-2,3,6,7-tetrahydrobenzo[1,2-*b*:4,5-*b'*]difuran-4-yl)-2-aminopropane ((R)-19). Toluene (25 mL) was added to a flask fitted with a Dean–Stark trap and containing tetramethylammonium trifluoroacetate (1.2 g, 6.3 mmol), copper iodide (1.4 g, 7.1 mmol), and (R)-17 (0.50 g, 1.3 mmol).¹⁵ This mixture was brought to reflux for 4 h to azeotrope residual H₂O present in the starting materials. Next, anhydrous DMF (7.9 mL, 101.5 mmol) was added slowly with concomitant removal of toluene to bring the reaction temperature to 145 °C for 4 h. The reaction was monitored by ¹⁹F NMR for the appearance of a second singlet. Upon completion, the reaction was cooled to room temperature, diluted with H₂O (100 mL) and extracted with CH₂Cl₂ (4 × 50 mL). The organic layers were combined, dried (MgSO₄), filtered, and evaporated to leave a white solid that was subjected to column chromatography (4:1 hexanes–ethyl acetate as eluent) to afford the title compound as white crystals: 0.35 g, 72%; mp 178–179 °C; ¹H NMR (CDCl₃) δ 1.28 (d, 3 H, CHCH₃, J = 6.3 Hz), 2.77 (t, 1 H, ArCH₂CH, J = 13.5

H_z), 2.78 (q, 1 H, ArCH₂CH, *J* = 12.9 Hz), 3.13 (t, 2 H, ArOCH₂CH₂, *J* = 8.7 Hz), 3.34 (t, 2 H, ArOCH₂CH₂, *J* = 8.7 Hz), 4.17 (m, 1 H, ArCH₂CH, *J* = 6.9 Hz), 4.59 (t, 2 H, ArOCH₂CH₂, *J* = 9.0 Hz), 4.67 (t, 2 H, ArOCH₂CH₂, *J* = 8.7 Hz), 7.40 (bs, 1 H, NH); [α]_D = +1.79° (*c* = 0.013, CH₃CN); CIMS *m/z* 384 (*M* + H⁺). Anal. (C₁₆H₁₅F₆NO₃) C, H, N.

(S)-(-)-*N*-Trifluoroacetyl-1-(8-trifluoromethyl-2,3,6,7-tetrahydrobenzo[1,2-*b*:4,5-*b'*]difuran-4-yl)-2-aminopropane ((S)-19). The title compound was prepared from (S)-17 by the procedure described for compound (R)-19: 70%; mp 178–179 °C; ¹H NMR (CDCl₃) δ 1.28 (d, 3 H, CHCH₃, *J* = 6.3 Hz), 2.77 (t, 1 H, ArCH₂CH, *J* = 13.5 Hz), 2.78 (q, 1 H, ArCH₂CH, *J* = 12.9 Hz), 3.13 (t, 2 H, ArOCH₂CH₂, *J* = 8.7 Hz), 3.34 (t, 2 H, ArOCH₂CH₂, *J* = 8.7 Hz), 4.17 (m, 1 H, ArCH₂CH, *J* = 6.9 Hz), 4.59 (t, 2 H, ArOCH₂CH₂, *J* = 9.0 Hz), 4.67 (t, 2 H, ArOCH₂CH₂, *J* = 8.7 Hz), 7.40 (bs, 1 H, NH); [α]_D = -1.83° (*c* = 0.013, CH₃CN); CIMS *m/z* 384 (*M* + H⁺). Anal. (C₁₆H₁₅F₆NO₃) C, H, N.

(R)-(-)-1-(8-Trifluoromethyl-2,3,6,7-tetrahydrobenzo[1,2-*b*:4,5-*b'*]difuran-4-yl)-2-aminopropane Hydrochloride ((R)-5a·HCl). The title compound was prepared from (R)-19 by the general procedure described for compound (R)-5a·HCl: 84%; mp 314–315 °C; ¹H NMR (D₂O) δ 1.27 (d, 3 H, CHCH₃, *J* = 7.2 Hz), 2.87 (m, 2 H, ArCH₂CH, *J* = 6.9 Hz), 3.18 (t, 2 H, ArOCH₂CH₂, *J* = 9.0 Hz), 3.33 (t, 2 H, ArOCH₂CH₂, *J* = 8.6 Hz), 3.69 (m, 1 H, ArCH₂CH, *J* = 6.6 Hz), 4.61 (q, 2 H, ArOCH₂CH₂, *J* = 8.7 Hz), 4.64 (q, 2 H, ArOCH₂CH₂, *J* = 8.7 Hz); [α]_D = -13.33° (*c* = 0.0097, DMF); CIMS *m/z* 288 (*M* + H⁺). Anal. (C₁₄H₁₇ClF₃NO₂) C, H, N.

(S)-(+)-1-(8-Trifluoromethyl-2,3,6,7-tetrahydrobenzo[1,2-*b*:4,5-*b'*]difuran-4-yl)-2-aminopropane Hydrochloride ((S)-5c·HCl). The title compound was prepared from (S)-19 by the general procedure described for compound (R)-5a·HCl: 84%; mp 314–315 °C; ¹H NMR (D₂O) δ 1.27 (d, 3 H, CHCH₃, *J* = 7.2 Hz), 2.87 (m, 2 H, ArCH₂CH, *J* = 6.9 Hz), 3.18 (t, 2 H, ArOCH₂CH₂, *J* = 9.0 Hz), 3.33 (t, 2 H, ArOCH₂CH₂, *J* = 8.6 Hz), 3.69 (m, 1 H, ArCH₂CH, *J* = 6.6 Hz), 4.61 (q, 2 H, ArOCH₂CH₂, *J* = 8.7 Hz), 4.64 (q, 2 H, ArOCH₂CH₂, *J* = 8.7 Hz); [α]_D = +12.90° (*c* = 0.0097, DMF); CIMS *m/z* 288 (*M* + H⁺). Anal. (C₁₄H₁₇ClF₃NO₂) C, H, N.

(R)-(+)-*N*-Trifluoroacetyl-1-(8-trifluoromethylbenzo[1,2-*b*:4,5-*b'*]difuran-4-yl)-2-aminopropane ((R)-20). The title compound was prepared from (R)-19 by the general procedure described for compound (R)-16: 74%; mp 170–171 °C; ¹H NMR (CDCl₃) δ 1.27 (d, 3 H, CHCH₃, *J* = 6.3 Hz), 3.35 (d, 2 H, ArCH₂CH, *J* = 6.0 Hz), 4.48 (m, 1 H, ArCH₂CH, *J* = 7.5 Hz), 6.39 (bs, 1 H, NH), 7.68 (d, 1 H, ArH, *J* = 2.4 Hz), 7.07 (p, 1 H, ArH, *J* = 1.8 Hz), 7.74 (d, 1 H, ArH, *J* = 2.4 Hz), 7.77 (d, 1 H, ArH, *J* = 2.1 Hz); [α]_D = +7.46° (*c* = 0.0025, CH₃CN); CIMS *m/z* 380 (*M* + H⁺), 360. Anal. (C₁₆H₁₁F₆NO₃) C, H, N.

(S)-(-)-*N*-Trifluoroacetyl-1-(8-trifluoromethylbenzo[1,2-*b*:4,5-*b'*]difuran-4-yl)-2-aminopropane ((S)-20). The title compound was prepared from (S)-19 by the general procedure described for compound (R)-16: 75%; mp 170–171 °C; ¹H NMR (CDCl₃) δ 1.27 (d, 3 H, CHCH₃, *J* = 6.3 Hz), 3.35 (d, 2 H, ArCH₂CH, *J* = 6.0 Hz), 4.48 (m, 1 H, ArCH₂CH, *J* = 7.5 Hz), 6.39 (bs, 1 H, NH), 7.68 (d, 1 H, ArH, *J* = 2.4 Hz), 7.07 (p, 1 H, ArH, *J* = 1.8 Hz), 7.74 (d, 1 H, ArH, *J* = 2.4 Hz), 7.77 (d, 1 H, ArH, *J* = 2.1 Hz); [α]_D = -7.38° (*c* = 0.0025, CH₃CN); CIMS *m/z* 380 (*M* + H⁺), 360. Anal. (C₁₆H₁₁F₆NO₃) C, H, N.

(R)-(-)-1-(8-Trifluoromethylbenzo[1,2-*b*:4,5-*b'*]difuran-4-yl)-2-aminopropane Hydrochloride ((R)-6c·HCl). The title compound was prepared from (R)-20 by the general procedure described for compound (R)-5a·HCl: 69%; mp 282 °C dec; ¹H NMR (D₂O) δ 1.28 (d, 3 H, CHCH₃, *J* = 6.6 Hz), 3.41 (d, 1 H, ArCH₂CH, *J* = 6.9 Hz), 3.42 (d, 1 H, ArCH₂CH, *J* = 6.3 Hz), 3.87 (m, 1 H, ArCH₂CH, *J* = 6.6 Hz), 7.08 (d, 1 H, ArH, *J* = 2.7 Hz), 7.13 (p, 1 H, ArH, *J* = 1.8 Hz), 7.87 (d, 1 H, ArH, *J* = 2.4 Hz), 7.90 (d, 1 H, ArH, *J* = 2.1 Hz); [α]_D = -33.49° (*c* = 0.0106, DMF); CIMS *m/z* 284 (*M* + H⁺). Anal. (C₁₄H₁₃ClF₃NO₂) C, H, N.

(S)-(+)-1-(8-Trifluoromethylbenzo[1,2-*b*:4,5-*b'*]difuran-4-yl)-2-aminopropane Hydrochloride ((S)-6c·HCl). The title compound was prepared from (S)-20 by the general

procedure described for compound (R)-5a·HCl: 71%; mp 283 °C dec; ¹H NMR (D₂O) δ 1.28 (d, 3 H, CHCH₃, *J* = 6.6 Hz), 3.41 (d, 1 H, ArCH₂CH, *J* = 6.9 Hz), 3.42 (d, 1 H, ArCH₂CH, *J* = 6.3 Hz), 3.87 (m, 1 H, ArCH₂CH, *J* = 6.6 Hz), 7.08 (d, 1 H, ArH, *J* = 2.7 Hz), 7.13 (p, 1 H, ArH, *J* = 1.8 Hz), 7.87 (d, 1 H, ArH, *J* = 2.4 Hz), 7.90 (d, 1 H, ArH, *J* = 2.1 Hz); [α]_D = +33.38° (*c* = 0.0106, DMF); CIMS *m/z* 284 (*M* + H⁺). Anal. (C₁₄H₁₃ClF₃NO₂) C, H, N.

Chromatographic Studies. All HPLC analyses were performed on a Rainin Rabbit HPX high-performance liquid chromatograph with a Knauer variable wavelength detector set to observe at 254 nm. A 20-μL injection loop was used for sample injection. A flow rate of 1 mL/min of dichloromethane was used as the mobile phase through a 250 × 4.6-mm Alltech Silica column. Chromatographic parameters reported for each solute are averages of triplicate analyses.

Representative Procedure for Amine Derivatization.²² *N*-Trifluoroacetyl-1-(8-bromo-2,3,6,7-tetrahydrobenzo[1,2-*b*:4,5-*b'*]difuran-4-yl)-2-aminopropane ((R or S)-17). To confirm that the samples of product (R)- and (S)-5b·HCl that were used in pharmacological evaluation were not contaminated with side products of the aromatic bromination reaction used to make (R or S)-17, a sample of (R)-5b·HCl was converted to the *N*-trifluoroacetyl-protected compound. Trifluoroacetic anhydride (0.010 mL, 0.072 mmol) was added dropwise to a dichloromethane (0.4 mL) solution of (R)-5b·HCl (0.010 g, 0.030 mmol), triethylamine (0.014 mL, 0.105 mmol) and 4-(dimethylamino)pyridine (0.0003 g, 0.0024 mmol). The reaction was stirred for 4 h and then diluted with dichloromethane (4 mL), washed with aqueous 2 N HCl (2 mL), saturated NaHCO₃ (2 mL), dried (MgSO₄), filtered, and evaporated to leave a clear oil. HPLC analysis of this oil indicated that it was 99.5% pure and had a retention time of 7.10 min (±0.01 min). This procedure was repeated for a sample of (S)-5b·HCl. HPLC analysis of this product indicated a 99.3% purity and a retention time of 7.11 min (±0.02 min). None of the minor impurities observed in the HPLC data trace corresponded to the fully aromatic compound (R)-18 which was likewise analyzed by HPLC and found to have a retention time of 4.98 min (±0.03 min) and a purity of 99.2%. These results indicate that careful addition of bromine to the reaction discussed above and recrystallization of the product led to pure compounds and that the pharmacological data were not confounded by potent impurities.

***N*-(1-Methyl-2-(8-trifluoromethylbenzo[1,2-*b*:4,5-*b'*]difuran-4-yl)ethyl)-(R)-MTPA Amides.** To confirm that the integrity of the chiral center remained intact throughout the reactions used in the synthetic scheme, of which several might have potentially racemized the stereocenter, products (R)- and (S)-6c·HCl were converted to their corresponding MTPA amides using (R)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride¹⁶ ((R)-MTPA-Cl: Fluka) to provide the pair of diastereomers for HPLC analysis. This was accomplished by the general procedure²² used to make the trifluoroacetyl-protected compound discussed above, using 2.4 equiv of (R)-MTPA-Cl in place of the trifluoroacetic anhydride. The oils that were obtained were dissolved in dichloromethane to give equal concentrations of each solute. To be certain baseline separation could be accomplished using the HPLC conditions discussed above, an equimolar mixture of the pure amides was prepared by combining equal volumes of the two amide solutions and performing HPLC analysis on this mixture. Excellent resolution was obtained, with approximately 2.2 min of baseline separation between the two eluted diastereoisomers. The 2*R*,1'*S*-amide was analyzed by HPLC and found to be 99.4% pure, with a retention time of 11.69 min (±0.03 min). A very small peak that corresponded to the 2*R*,1'*R*-amide was observed however, which accounted for the other 0.6% of the injected sample. The 2*R*,1'*R*-amide was also analyzed by HPLC and found to be 100.0% pure, with a retention time of 13.95 min (±0.01 min). These results indicated that racemization had not occurred in the synthesis of these products. Further, because products (R)- and (S)-6c·HCl were subjected to all possible reaction conditions in the synthetic scheme, one may

deduce that all the other products are likewise enantiomerically pure. The small amount of the 2*R*,1'*R*-amide found in the 2*R*,1'*S*-amide most likely arose as a consequence of the slightly lower purity of the L-alanine starting material.

Pharmacology Methods. 1. Cell Culture. NIH-3T3 fibroblast cells stably transfected to express either the rat 5-HT_{2A} or 5-HT_{2C} receptor²³ were maintained in minimum essential medium, containing 10% dialyzed fetal bovine serum (Gibco BRL) and supplemented with L-glutamine, Pen/Strep, and Geneticin. The cells were cultured at 37 °C in a water saturated atmosphere of 95% air and 5% CO₂. For radioligand binding assays, cells were split into 100-mm² culture dishes when they reached 90% confluency. Upon reaching 100% confluency in the culture dishes, the cells were washed with sterile filtered phosphate-buffered solution and left to incubate in serum-free Opti-MEM for 5 h. After this incubation, the cells were harvested by centrifugation (15000*g*, 20 min) and placed immediately in a freezer at -80 °C until the assay was performed. For phosphoinositide hydrolysis experiments the cells were seeded into 24-well plates and assays were performed when 70% confluency was achieved.

2. Radioreceptor Competition Assays. For saturation assays, 0.125–6 nM [³H]DOB or [¹²⁵I]DOI were used. The total volume of the assay was 250 μL. Nonspecific binding was defined in the presence of 10 μM cinanserin (rat 5-HT_{2A}-expressing cells) or 10 μM mianserin (rat 5-HT_{2C}-expressing cells). Competition binding experiments were carried out in a total volume of 500 μL with either 1.0 nM [³H]DOB or 0.20 nM [¹²⁵I]DOI. Previously harvested cells were resuspended and added to each well containing assay buffer (50 mM Tris, 0.5 mM EDTA, 10 mM MgCl₂; pH = 7.4), radioligand, and new compound (or in the case of the saturation assays, cinanserin or mianserin). Incubation was carried out at 25 °C for 60 min and terminated by rapid filtration using a prechilled Packard 96-well harvester with GF/B Uni-filters that had been preincubated for 30 min in 0.3% polyethylenimine. The filters were rinsed using chilled wash buffer (10 mM Tris, 154 mM NaCl) and left to dry overnight. The following day, Microscint-O was added and radioactivity was determined using a TopCount (Packard) scintillation counter. GraphPad Prism (GraphPad Software, San Diego, CA) was used to analyze the saturation and competition binding curves.

3. Phosphoinositide Hydrolysis Studies in NIH-3T3 Cells Expressing the 5-HT_{2A} Receptor. Accumulation of inositol phosphates was determined using a modified version of a previously published protocol.²⁴ Briefly, cells expressing the rat 5-HT_{2A} receptor were labeled for 18–20 h in CRML medium containing 1.0 μCi/mL [³H]myo-inositol. After pre-treating the cells with 10 μM pargyline/10 mM LiCl for 15 min, the cells were placed in the presence of agonist for 30 min at 37 °C, under an atmosphere of 95% O₂ and 5% CO₂. The assay was terminated by aspirating the medium and adding 10 mM formic acid. After incubation for 16 h at 4 °C, the [³H]inositol phosphates were separated from the cellular debris on Dowex-1 ion-exchange columns and eluted with 1.0 M ammonium formate and 0.10 M formic acid. The vials were counted for tritium using a TriCarb scintillation counter (Packard Instrument Corp.).

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References

- Sanders-Bush, E.; Mayer, S. E. 5-Hydroxytryptamine (Serotonin) Receptor Agonists and Antagonists. In *The Pharmacological Basis of Therapeutics*, 9th ed.; Hardman, J. G., Limbird, L. E., Molinoff, P. B., Ruddon, R. W., Gilman, A. G., Eds.; McGraw-Hill: New York, 1996; pp 249–263.
- Aghajanian, G. K.; Marek, G. J. Serotonin-Glutamate Interactions: A New Target for Antipsychotic Drugs. *Neuropsychopharmacology* **1999**, *21*, S122–S133.
- Roth, B. L.; Willins, D. L.; Kristiansen, K.; Kroeze, W. K. 5-Hydroxytryptamine₂-Family Receptors (5-Hydroxytryptamine_{2A}, 5-Hydroxytryptamine_{2B}, 5-Hydroxytryptamine_{2C}): Where Structure Meets Function. *Pharmacol. Ther.* **1998**, *79*, 231–257.
- Boess, F. G.; Martin, I. L. Molecular Biology of 5-HT Receptors. *Neuropharmacology* **1994**, *33*, 275–317.
- Monte, A. P.; Marona-Lewicka, D.; Kanthasamy, A.; Sanders-Bush, E.; Nichols, D. E. Stereoselective LSD-like Activity in a Series of d-Lysergic-Acid Amides of (*R*)-2-Aminoalkanes and (*S*)-2-Aminoalkanes. *J. Med. Chem.* **1995**, *38*, 958–966.
- Oberlender, R.; Ramachandran, P. V.; Johnson, M. P.; Huang, X.; Nichols, D. E. Effect of a Chiral 4-Alkyl Substituent in Hallucinogenic Amphetamines. *J. Med. Chem.* **1995**, *38*, 3593–3601.
- Monte, A. P.; Waldman, S. R.; Marona-Lewicka, D.; Wainscott, D. B.; Nelson, D. L.; Sanders-Bush, E.; Nichols, D. E. Dihydrobenzofuran Analogues of Hallucinogens. 4. Mescaline Derivatives. *J. Med. Chem.* **1997**, *40*, 2997–3008.
- Parker, M. A.; Marona-Lewicka, D.; Lucaites, V. L.; Nelson, D. L.; Nichols, D. E. A Novel (Benzodifuranyl)aminoalkane with Extremely Potent Activity at the 5-HT_{2A} Receptor. *J. Med. Chem.* **1998**, *41*, 5148–5149.
- Parker, M. A. Studies of Perceptiotropic Phenethylamines: Determinants of Affinity for the 5-HT_{2A} Receptor. Ph.D. Thesis, Purdue University, 1998.
- Blade-Font, A.; Rocabayera, T. M. Synthesis of Dihydrobenzofurans from Phenolic Mannich Bases and their Quaternized Derivatives. *J. Chem. Soc., Perkin Trans. 1* **1982**, *38*, 841–848.
- Monte, A. P.; Marona-Lewicka, D.; Parker, M. A.; Wainscott, D. B.; Nelson, D. L.; Nichols, D. E. Dihydrobenzofuran Analogues of Hallucinogens. 3. Models of 4-Substituted (2,5-Dimethoxyphenyl)alkylamine Derivatives with Rigidified Methoxy Groups. *J. Med. Chem.* **1996**, *39*, 2953–2961.
- Curphey, T. J. Trifluoroacetylation of Amino Acids and Peptides by Ethyl Trifluoroacetate. *J. Org. Chem.* **1979**, *44*, 2805–2807.
- Nordlander, J. E.; Payne, M. J.; Njoroge, F. G.; Balk, M. A.; Laikos, G. D.; Vishwanath, V. M. Friedel-Crafts Acylation with *N*-(Trifluoroacetyl)-α-amino Acid Chlorides. Application to the Preparation of β-Arylalkylamines and 3-Substituted 1,2,3,4-Tetrahydroisoquinolines. *J. Org. Chem.* **1984**, *49*, 4107–4111.
- Moron, J.; Bisagni, E. Synthesis of 4-Methylfuro[3',2':5,6]benzofuro[3,2-*c*]pyridine. *J. Heterocycl. Chem.* **1986**, *23*, 1637–1639.
- Carr, G. E.; Chambers, R. D.; Holmes, T. F.; Parker, D. G. Sodium Perfluoroalkane Carboxylates as Sources of Perfluoroalkyl Groups. *J. Chem. Soc., Perkin Trans. 1* **1988**, *38*, 921–926.
- Dale, J. A.; Dull, D. L.; Mosher, H. S. α-Methoxy-α-trifluoromethylphenylacetic Acid, a Versatile Reagent for the Determination of Enantiomeric Composition of Alcohols and amines. *J. Org. Chem.* **1969**, *34*, 2543–2549.
- Makriyannis, A.; Knittel, J. Conformational-Analysis of Amphetamine in Solution Based on Unambiguous Assignment of the Diastereotopic Benzylic Protons in the H-1-NMR Spectra. *Tetrahedron Lett.* **1981**, *22*, 4631–4634.
- Nichols, D. E.; Frescas, S.; Marona-Lewicka, D.; Huang, X.; Roth, B. L.; Gudelsky, G. A.; Nash, J. F. 1-(2,5-Dimethoxy-4-(trifluoromethyl)phenyl)-2-aminopropane – A Potent Serotonin 5-HT_{2A/2C} Agonist. *J. Med. Chem.* **1994**, *37*, 4346–4351.
- Siubasma, R. P.; Nolte, R. J. M. Synthesis of Concave Receptors Derived from Diphenylglycoluril. *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 643–647.
- Ellison, R. A.; Kotsonis, F. N. Complexation as a Factor in Metalation Reactions. Metalation of 1-Methoxy-2-phenoxyethane. *J. Org. Chem.* **1973**, *38*, 4192–4196.
- Alabaster, R. J.; Cottrell, I. F.; Marley, H.; Wright, S. H. B. The synthesis of 5-Substituted 2,3-Dihydrobenzofurans. *Synthesis* **1988**, 950–952.
- Jackson, P. T.; Kim, T.-Y.; Carr, P. W. Diastereomeric Selectivity of Carbon-Coated Zirconia Reversed-Phase Liquid Chromatographic Media. *Anal. Chem.* **1997**, *69*, 5011–5017.
- Julius, D.; Huang, K. N.; Livelli, T. J.; Axel, R.; Jessell, T. M. The 5HT₂ receptor defines a family of structurally distinct but functionally conserved serotonin receptors. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 928–932.
- Berg, K. A.; Clarke, W. P.; Sailstad, C.; Saltzman, A.; Maayani, S. Signal Transduction Differences Between 5-Hydroxytryptamine Type 2A and Type 2C Receptor Systems. *Mol. Pharmacol.* **1994**, *46*, 477–484.

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